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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,378	12/27/2001	Walter Muller	512100-2024	6397

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EXAMINER

GHALI, ISIS A D

ART UNIT	PAPER NUMBER
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1615

DATE MAILED: 12/01/2003

7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,378	MULLER, WALTER	
	Examiner	Art Unit	
	Isis Ghali	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 September 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11-28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>3</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The receipt is acknowledged of applicant's request for extension of time and amendment A, both filed 09/12/2003.

Claims 1-10 have been canceled, and claims 11-28 have been added and included in the prosecution.

1. The standing rejections:

Claim Rejections - 35 USC § 103

(A) Claims 11-14, 16-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 87/07138 ('138) in view of US 5,071,657 ('657).

WO '138 teaches a transdermal absorption dosage unit comprising substantially impervious backing layer, a layer of polymer matrix in which a drug is microdispersed (reads on microreservoirs); an adhesive means for securing the dosage unit to the skin of the treated subject; and a release liner (abstract; page 19, line 25; page 35, lines 1-40). The polymer matrix is made from polysiloxane polymer or polydimethylsiloxane, applicant claims polysiloxanes in general (page 5, lines 24-31; page 36, lines 10-12). The pharmaceutical agents are dissolved in a selected solvent (page 16, lines 51-56). The amount of the solvent is between 0 - 50% by weight of the polymer matrix (page 16, lines 14-21). The polydimethylsiloxane polymer forms 70 parts of the polymer matrix

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(page 17, lines 25-31). Thus, the amounts of the solvent and polysiloxane polymers are met by the reference. The thickness of the polymer matrix layer is 0.05 mm to 5 mm (50-5000 micron), and the microdispersed compartments (microreservoirs) have cross-sectional dimensions of 10-200 micron (page 17, lines 50-56; page 36, lines 45-53). Thus, the maximum size of the microreservoirs (200 micron) does not exceed 80% of the thickness of the polymer matrix layer (that can be up to 4000 micron), and this meets the limitation of claim 8. The reference disclosed a process for the manufacture of the polymer matrix that includes dissolving and dispersing the drug in the solvent, and then mixing the dispersion with the polysiloxane polymer to form microdispersion, then heating to temperature of 20° C 100° C to form the polymer sheet that can be formed directly on the backing sheet (page 16, lines 50-56; page 17, lines 1-6, 40-51; page 18, lines 6-10). This method of manufacture does not include water and that means that the microreservoirs will be essentially free from water, and that meets the limitation of claim 3. It is expected for the polysiloxane polymer to have the same physical properties such as adhesiveness, and that meets claim 4 because the filler recited in claim 4 is only an optional component.

The reference, however, does not teach specifically the ambiphilic solvents and their physical properties (as recited in component (c) and (d) of claims 1, and claims 6 and 7), and does not teach that the microreservoirs comprise crystallization inhibitor, viscosity increasing agent and/or pH regulator (claim 9).

US '657 teaches a device for transdermal administration of active medicinal agent dissolved in a nonflowable gel that form microdispersion (microreservoirs) in a

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silicone elastomer (abstract). The nonflowable gel comprises a thickener, i.e. viscosity increasing agent (claim 9), and solvent that has boiling point of 80⁰ C or higher (col.2, lines 41-45). These solvents include propylene glycol, and diethylene glycol and ethers thereof, i.e. ambiphilic solvents claimed in claims 1 (c) and 6 (col.2, lines 53-57). It is expected that the solvents disclosed by the reference would have the same physical properties as claimed by applicant in claims 1 (d), 6 and 7, i.e. solubility in polysiloxane, miscibility with water, being in liquid state at room temperature and having higher boiling point than the boiling point of the solvent for the polysiloxane. The solvents are sufficiently lipophilic to dissolve the medicine, and on the other hand, are adequately hydrophilic to provide the desired active agent transport through the skin (col.2, lines 46-49).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a transdermal therapeutic system comprising a polymer layer comprising polysiloxane and microreservoirs containing the active substance and a solvent as disclosed by WO '138, and replace the solvent disclosed by the WO '138 by any of the solvents disclosed by US '657 because the solvents disclosed by US '657 are sufficiently lipophilic to dissolve the medicine, and on the other hand, are adequately hydrophilic to provide the desired active agent transport through the skin, with reasonable expectation of having a transdermal therapeutic system with dissolved active substances ready to transport across the skin with success.

Response to Arguments:

- 1) WO 138 teaches polyols, such as polyethylene glycol, as dispersing agent and not dissolving agent.
- 2) WO '138 teaches the amount of the dispersing agent is from 0-50, and when the amount of zero the transdermal dosage unite comprises solid polymer with dispersed solid active agent; and when the amount is from 10-50 this results in fluid/solid dispersion.
- 3) WO '138 used cross-linked silicon elastomer, not polysiloxanes as the present invention.
- 4) WO '138 teaches that part of the drug is undissolved, while applicant's disclosure is dissolved active substance.
- 5) While applicant admits that the US '657 teaches the same solvent, yet argues that the reference teaches active agent dissolved to at least 50% in gel present in micro dispersion distribution in cross-linked silicone elastomer. Applicant's polymer behaves like viscous fluid, not gel.
- 6) The rejection does not establish a *prima facie* case of obviousness since the WO '138 does not teach TTS wherein the active agents are located in micro reservoir and US '657 does not teach polysiloxane.

Examiner's Position:

Applicant's arguments filed 09/12/2003 have been fully considered but they are not persuasive.

- 1) WO '138 disclosed the generic teaching of polyols as a dispersing agent for the drug, as well as dissolving agent to the drug (page 16, lines 50-55).
- 2) WO '138 teaches that the solubility of the drug varies by the amount of the polyols, thus in the amount of zero the drug is solid, with increasing the amount the solubility will increase. It is known to the skilled artisan that different drugs have different solubility in different solvents, and it within the skill in the art to select the amounts of different solvent to obtain the desired consistency of the composition. The reference also disclosed that the dispersion forms micro-compartment that have the same dimension as claimed by applicant. Thus, it is not simple dispersion, but micro-compartments or reservoirs.
- 3) WO '138 disclosed polysiloxane as a species of medical grade silicone (page 5, lines 29-30; page 17, lines 29-31; claim 10).
- 4) WO '138 teaches both dissolved and dispersed drug. The expression comprising of the claim language permits the presence of the undissolved drugs.
- 5) US '657 is relied upon for teaching the specific species of the solvent that dissolve the steroidal drugs. The reference also teaches the polysiloxanes and the micro-dispersion. The claims are directed to a composition and the intended use of the

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composition as a gel or viscous fluid does not impart patentability to the composition claims.

6) *Prima facie* case of obviousness is established because the WO '138 teaches the two element of the product: the solvent and the polysiloxane and the solvent that causes the micro-reservoirs (micro dispersion) that have the same dimension as disclosed by the applicant. The secondary reference teaches the species of the solvent. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a transdermal therapeutic system comprising a polymer layer comprising polysiloxane and micro reservoirs containing the active substance and a solvent as disclosed by WO '138, and replace the solvent disclosed by the WO '138 by any of the solvents disclosed by US '657 because the solvents disclosed by US '657 are sufficiently lipophilic to dissolve the medicine, and on the other hand, are adequately hydrophilic to provide the desired active agent transport through the skin, with reasonable expectation of having a transdermal therapeutic system with dissolved active substances ready to transport across the skin with success.

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(B) Claims 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO '138 in view of US '657 as applied to claims 1, and 3-10 above, and further in view of US 5,145,682 ('682).

WO '138, as discussed above, teaches a transdermal absorption dosage unit comprising backing layer, a layer of polysiloxane polymer matrix in which a drug is microdispersed; an adhesive means for securing the dosage unit to the skin of the treated subject; and a release liner, wherein the active substance is in the dissolved form. The reference also disclosed a process for the manufacture of the TTS. US '657 teaches the ambiphilic solvents.

The references in combination, however, do not teach the polysiloxane polymer to be amine-resistant (claim 15).

US '682 disclosed a transdermal absorption dosage unit comprising an impervious backing; an adhesive polymer layer of silicone adhesive comprising microreservoirs encapsulating the active substance; additional adhesive layer; a releasable protective film layer (abstract; col.3, lines 118-19, 56; col.7, lines 30-31). Amine-resistant adhesive polymers are suitable for use in making the adhesive polymer layer such as BIO-PSA, used by applicant in their examples, because they are biologically acceptable and chemically compatible with the pharmaceutical substances (col.6, lines 40-64).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a transdermal therapeutic system comprising a

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polymer layer comprising polysiloxane and microreservoirs containing the active substance and an ambiphilic solvent as disclosed by WO '138 in view of US '657, and replace the polysiloxane by the amine-resistant polysiloxane as taught by the US '682 because US '682 teaches that the amine resistant polysiloxane are biologically acceptable and chemically compatible with the pharmaceutical substances with reasonable expectation of having a safe transdermal therapeutic system with dissolved active substances ready to transport across the skin with success.

Response to Arguments

Applicant argue that the rejection of claim 2 is improper and does not correct the deficiencies of WO '138 and US '657.

Examiner's Position:

US '682 is relied upon for the solely teaching that the amine-resistant polysiloxanes are known and used in the transdermal devises as they are biologically acceptable and chemically compatible with pharmaceutical substances.

Conclusion

2. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis Ghali whose telephone number is (703) 305-4048. The examiner can normally be reached on Monday through Thursday from 7:00 AM to 5:30 PM, Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

Isis Ghali
Examiner
Art Unit 1615

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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